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CORRESPONDENCE

Letters to the Editor

Exclusive Antiplatelet Therapy for Percutaneous Coronary Intervention

A journey of a thousand miles begins with a single step.
—Lao Tzu, ancient Chinese philosopher (1)

Stabile et al. (2) indeed deserve congratulations for the clinical trial that they recently published in the *Journal*. It is the first step on a journey into exclusive dual antiplatelet therapy (aspirin and clopidogrel) alone during percutaneous coronary intervention (PCI), without scheduled antithrombin or glycoprotein inhibitor therapy. However, as pointed out in the accompanying editorial by Dauerman (3), there are several concerns with the trial. Specifically, the approach of dual antiplatelet therapy alone may lack an essential "safety net" that could be provided by antithrombin therapy or, perhaps, glycoprotein inhibitor therapy.

Thrombosis during PCI and otherwise occurs through 2 interrelated mechanisms: first, the adhesion, activation, secretion, and aggregation of platelets; and second, amplification of the coagulation cascade, which requires an activated platelet surface for the development of thrombin (4). In theory, if adequate antiplatelet therapy is provided, thrombosis will not occur, even in the absence of antithrombin therapy directed towards the coagulation cascade. This theory has been supported by in vitro experiments dating back over 20 years (5).

Subsequent clinical research published 15 years ago involving a new class of drug, the glycoprotein IIb/IIIa inhibitors (e.g., abciximab), which block the final common pathway of platelet aggregation, showed a significant decrease in ischemic complications during PCI at the expense of a significant increase in bleeding complications (6). These results created a dilemma for those interventional cardiologists (including myself) who already had a relatively high bleeding complication rate (7). Therefore, 12 years ago, in an effort to optimize patient care, I changed from the then contemporary combination of dual antiplatelet therapy (aspirin and ticlopidine) and a conventional dose of unfractionated heparin to triple antiplatelet therapy (adding abciximab) and only a minimal dose of unfractionated heparin. The success of this approach (8) led me to take one step further 9 years ago to exclude scheduled antithrombin therapy altogether for both elective, low risk and urgent, higher risk PCI, while relying on triple antiplatelet therapy (aspirin, clopidogrel, and eptifibatide) alone (9,10). Despite the success of this strategy in limiting both ischemic and bleeding complications, and despite subsequent support provided by REMOVE (Reduction in Major and Minor Adverse Events With Eptifibatide-based Pharmacotherapy in Percutaneous Coronary Intervention) (11), exclusive antiplatelet therapy drew skepticism and criticism from many of our cardiovascular colleagues. The trial published by Stabile et al. (2) therefore provided timely and much needed support for the "exclusive antiplatelet therapy" proponents.

Stabile et al. (2), however, was confined to very low-risk PCI, and the safety net concern expressed by Dauerman (3) poses a valid question. On the basis of theory, in vitro experiments and my own experiences, I believe that the safety net can be provided by glycoprotein IIb/IIIa receptor inhibition, using abciximab, eptifibatide, or, perhaps, tirofiban. This approach of triple antiplatelet therapy with minimal or no specific antithrombin therapy directed towards the coagulation cascade during PCI will, in my opinion, prove to be safe and efficacious for both elective, low-risk and urgent, higher-risk PCI. Hopefully, this approach will be proved by unbiased, well-designed randomized clinical trials that continue the journeys initiated by the proponents of "exclusive antiplatelet therapy" during PCI, including Stabile et al. (2)

***Scott J. Denardo, MD**

*Division of Cardiovascular Medicine
University of Florida
1600 SW Archer Road
P.O. Box 100277
Gainesville, Florida 32610
E-mail: scott.denardo@medicine.ufl.edu

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during elective percutaneous coronary intervention (the REMOVE trial). Am J Cardiol 2007;100:1099–102.

Reply

We would like to thank Dr. Denardo for his interest in our work (1), and we appreciate his quoting a proverb that well depicts our paper's take-home message. The CIAO (Coronary Interventions Antiplatelet-based Only) trial is a first step on a journey into exclusive dual antiplatelet therapy (aspirin and thienopyridine) alone during percutaneous coronary intervention (PCI), without scheduled antithrombin or glycoprotein inhibitor therapy.

We disagree with the accompanying editorial (2), which states that dual antiplatelet therapy alone may lack an essential "safety net" that could be provided by antithrombin therapy or, perhaps, glycoprotein inhibitor therapy. As pointed out by Dr. Denardo, the use of aspirin, combined with adequate patient pretreatment with a thienopyridine, will guarantee an adequate inhibition of platelet activity and lack of triggering for the coagulation cascade during a planned PCI (3,4).

Moreover, the use of the glycoprotein IIb/IIIa inhibitors (e.g., abciximab) will not add a further inhibition of the the final common pathway of platelet aggregation in stable patients in chronic treatment with thienopiridine. Solid clinical data proving the opposite are still lacking.

So far, the the only proof of this theory is the absence of thrombotic occlusions and the lower ischemic complications during PCI (i.e., periprocedural myocardial damage) in the placebo group of the CIAO trial (1).

An additional point is related to procedural costs. Our approach is aimed at a safe and efficient removal of expensive, unnecessary drugs from elective procedures. This is valid, both for inhibitors of the anticoagulation cascade, and for glycoprotein IIb/IIIa receptor inhibitors. We truly believe that these drugs, in this clinical setting, can only increase the incidence of bleeding and raise the costs without improving the patient's outcome.

However, as pointed out by Dr. Denardo, further trials are needed to make a second step along this path. Testing our hypothesis for the treatment of more complicated lesions is crucial to prove the clinical value of CIAO findings.

Finally, we want to thank Dr. Denardo, who has inspired our work. Thanks to his pioneering experience, together with the results of the REMOVE (Reduction in Major and Minor Adverse Events With Eptifibatide-based Pharmacotherapy in Percutaneous Coronary Intervention) (5) and CIAO (1) trials, exclusive antiplatelet therapy is not considered heretical any more.

***Eugenio Stabile, MD, PhD**
Paolo Rubino, MD

*Cardiac Catheterization Laboratories
Division of Cardiology
Clinica Montevergine
Via Mario Malzoni 1
Mercogliano AV 83013
Italy
E-mail: geko50@hotmail.com

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Reply

Well some things you can explain away,
but the heartache's in me till this day.

—The Clash, 1979 (1)

I read with interest Dr. Denardo's letter concerning the CIAO (Coronary Interventions Antiplatelet-based Only) trial (2) and the accompanying editorial (3). My congratulations are extended to Dr. Denardo and other investigators who have found novel approaches to reducing bleeding complications associated with percutaneous coronary intervention (PCI), including the CIAO approach, fondaparinux, bivalirudin, reduced doses of unfractionated heparin, improved femoral access technique, or radial artery approaches. As discussed in the editorial (3), caution is warranted when data are limited to selected lower-risk patient subsets.

Dr. Denardo's letter, though, focuses congratulations on the CIAO trial as a "first step on a journey into exclusive dual antiplatelet therapy." As expressed in the editorial, there are pathophysiologic concerns about embarking on this journey in higher-risk subgroups of patients. Specifically, concern arises with the statement: "if adequate antiplatelet therapy is provided, thrombosis will not occur, even in the absence of antithrombin therapy. . . ." Arguments against this hypothesis are the following:

- During the REMOVE (Reduction in Major and Minor Adverse Events With Eptifibatide-based Pharmacotherapy in Percutaneous Coronary Intervention) trial, thrombus did form during bifurcation PCI despite aspirin, clopidogrel, and glycoprotein inhibition (GPI). Thus, the protocol was amended to exclude these higher-risk lesions from a no-antithrombin approach (4).
- Platelet activation is induced by vessel injury, exposure to collagen, and a myriad of other agents. No antiplatelet agent that is clinically available can inhibit all pathways of platelet activation (5). Further, although GPI decreases platelet aggregation and the quantity of platelets in a growing thrombus, it may not prevent platelet adherence or platelet–leukocyte aggregation that can contribute to thrombin formation (6).
- Nonplatelet blood elements, particularly monocytes, support thrombin generation (7). The exclusive antiplatelet therapy approach would not necessarily prevent nonplatelet-mediated generation of thrombin.